REMARKS

Claims 1, 7-9, 40, and 42-49 are pending in the instant application. By this amendment, original Claim 4 has been re-instated, and Claims 1, 7, and 8 have been amended to clarify the invention by deletion of the term "tumor-specific antigen" and addition of "an antigen overexpressed in a cancer cell relative to its expression in a noncancerous cell of said cell type, with the proviso that the antigenic molecule is other than prostate-specific antigen" (PSA). The amendments of Claims 1, 7, and 8 reinstate the language of the claim as originally filed, with the additional proviso that PSA be excluded from the genus of antigenic molecules used in the claimed compositions.

Written description support for the amendments to Claims 1, 7, and 8 is found in the specification as originally filed (for example, at p. 8, *l.* 13, to p. 8, *l.* 5, and original Claims 6, 7, and 3, and p. 37, *l.* 19). Support for the proposition that claims can be properly amended to exclude a particular species of a genus is found in Section 2173.05(i) of the Manual of Patent Examining Procedure (MPEP) Eighth Edition, Revised February, 2003, as discussed further hereinbelow.

Thus, Claims 1, 4, 7-9, 40, and 42-49 will be pending upon entry of the instant application. As such, no new matter has been added by the instant amendment. Applicants respectfully request that the amendment and remarks made herein be entered into the record of the instant application.

1. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

The rejection of claims 1, 7-9, 40, and 42-49 under 35 U.S.C. § 112, first paragraph, for lack of enablement, has been maintained, with the Examiner alleging that the

specification does not enable the full scope of the claimed compositions. In particular, the Examiner has maintained his rejection with respect to Points 5 and 6 of Paper No. 13 (the Office Action mailed January 30, 2003), contending that one skilled in the art would be forced to do undue experimentation to determine the antigen to be used (Point 5), and to determine how to prevent diseases such as cancer and HIV (Point 6). Applicants respectfully disagree, for the reasons discussed below.

With respect to Point 5, Applicants submit that the skilled practitioner would be able to choose appropriate antigenic molecules to prepare and use the claimed compositions without undue experimentation. The skilled artisan would understand from reading the specification that the antigenic molecule required by the claims is capable of inducing an immune response, displaying the antigenicity of either (i) an antigen of an infectious agent of an infectious disease or (ii) an antigen overexpressed in a cancer cell relative to its expression in a noncancerous cell. According to the specification,

> .... when complexes formed between alpha (2) macroglobulin and an antigenic molecule having the antigenicity of a cancer cell antigen or of a pathogen, such alpha (2) macroglobulin–antigenic molecule complexes can be used to stimulate a cytotoxic T cell response directed against the alpha (2) macroglobulin incorporated antigen. Such complexes can be used as immunotherapeutic agents to treat cancer and infectious disease.
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> Specification, at p. 14, *ll*. 20-25

Using the methods described in the specification and known in the art, the skilled practitioner could readily select an antigen displaying the required antigenicity of a cancer cell antigen or an agent of an infectious disease, prepare an alpha (2) macroglobulin - antigenic molecule complex, and test it for immunogenicity without resorting to undue experimentation. Numerous examples of infectious disease antigens and antigens which are overexpressed in cancer cells were known in the art at the time of filing of the instant

application, examples of which are provided by the instant application (see, *e.g.*, Sections 5.2.4.1, 5.2.4.4 and 5.2.4.5), for example, at page 37, *ll.* 12-24:

> Preferably, where it is desired to treat or prevent cancer, known tumor-specific antigenic molecules or fragments or derivatives thereof are used. For example, such tumor specific or tumor-associated antigenic molecules include but are not limited to KS 1/4 pan-carcinoma antigen (Perez and Walker, 1990, J. Immunol. 142:3662-3667; Bumal, 1988, Hybridoma 7(4):407-415); ovarian carcinoma antigen (CA125) (Yu, et al., 1991, Cancer Res. 51(2):468-475); prostatic acid phosphate (Tailer, et al., 1990, Nucl. Acids Res. 18(16):4928); . . . melanoma-associated antigen p97 (Estin, et al., 1989, J. Natl. Cancer Inst. 81(6):445-446); melanoma antigen gp75 (Vijayasardahl, et al., 1990, J. Exp. Med. 171(4):1375-1380); high molecular weight melanoma antigen (Natali, et al., 1987, Cancer 59:55-63) and prostate specific membrane antigen.

Methods for determining the immunogenicity or antigenicity of such molecules, and methods for identifying immunogenic epitopes on such molecules are also commonly known in the art; the level of skill in this field is highly sophisticated. For example, there are numerous methods for determining the immunogenicity or antigenicity of any putative antigen are taught in the specification, and references for such methods are disclosed (see specification, *e.g.*, at p. 38, *ll.* 13-28 and p. 48, *l.*1 to p. 49, *l.*19). Methods for monitoring the effects of immunotherapy and determining dosage regimens are also well known, and provided therein (see specification at Sections 5.3, p. 41, *ll.* 9 to p. 47, *l.* 33 and p. 49, *l.* 20 to p. 51, *l.* 22; and Section 5.7).

Using these methods, the skilled practitioner could readily select an antigen molecule displaying the required antigenicity and prepare an alpha (2) macroglobulin complex, and test it for immunogenicity. To the extent that testing is necessary (*e.g.*, for determining the immunogenicity of a particular antigen, to monitor the effects of immunotherapy, or to determine the dosage regimen), such testing would have been routine to the skilled practitioner, and would therefore not require any undue experimentation.

For evidence of the asserted utility of the claimed compositions, Applicants invite the Examiner's attention to the Declaration of Pramod K. Srivastava under 37 C.F.R. § 1.132 ("the Srivastava Declaration"), which presents the results of an experiment which utilized a mouse model system to test the efficacy of purified complexes comprising alpha (2) macroglobulin and an antigenic molecule displaying the antigenicity of an antigen overexpressed in a cancer cell (relative to a noncancerous cell) in the treatment and prevention of cancer.

Paragraphs 7 through 9 of the Srivastava Declaration describe the use of non-covalent alpha (2) macroglobulin- OVA20 peptide complexes generated using synthetic OVA20 peptide containing the CTL epitope of ovalbumin ("OVA"), a protein which, in this model system, is specifically expressed in tumor cells, but not in any other cell of the mice.[1] In this experiment, mice were administered the non-covalent complexes, then challenged with tumor cells expressing OVA. The results shown in Figure 1 demonstrate that alpha (2) macroglobulin complexed to the OVA20 antigen interfered with tumor growth in mice challenged with tumors expressing OVA, and further show that, in certain individual mice, *no* tumor growth was observed, even 22 days after immunization with alpha (2) macroglobulin-OVA20 complexes. These results clearly demonstrate that the alpha (2) macroglobulin-antigenic molecule complexes can effectively delay the onset of tumor growth, and/or prevent tumor growth, indicating the efficacy of non-covalent complexes of alpha (2) macroglobulin and antigenic molecules in treating and preventing cancer.

The Examiner contends, however, that there are hundreds if not thousands of antigenic molecules that display antigenicity of a cancer antigen or infectious disease antigen,

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[1] The data presented in Paragraph 10 of the Declaration of Dr. Pramod Srivastava is identical to that presented in Figure 2b of Binder *et al.*, 2002 Cancer Immunity 2:16 ("EI") of the Information Disclosure Statement), however additional explanation of the results relevant to prevention of cancer is presented in the Declaration.

and that knowing which ones are effective in treatment is critical to the use of the instant invention. This is simply not the appropriate legal standard for enablement.

The Court of Appeals for the Federal Circuit ("Federal Circuit") has unambiguously held that determining efficacy in treating cancer is not required for compliance with enablement requirement of Section 112. *In re Brana,* 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Federal Circuit emphatically reversed the Board's decision affirming a final rejection under Section 112, first paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because the specification did not sufficiently establish that the claimed compounds had a practical utility as anti-tumor agents. *Id.* at 1439.

First, the *Brana* Court clarified the legal standard for compliance with the enablement requirement of Section 112 requirement, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support," a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* at 1441 (emphasis in the original). Further, it made clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of utility; evidence must be presented that those of skill in the art would doubt the disclosure. Only then must the applicant provide rebuttal evidence.

Second, the Federal Circuit explained that even if one of skill in the art would have questioned the asserted utility, *all applicants need do to overcome the rejection is to proffer sufficient evidence to convince one skilled in the art of the asserted utility. Id.* at 1441. The Federal Circuit further reminded the Commissioner that testing for the full safety and effectiveness of a product is more properly left to the Food and Drug Administration and the requirements under the law for obtaining a patent should not be confused with the

requirements for obtaining government approval to market a particular drug for consumption. *Id.* at 1442; see, *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994).

Thus, in view of the legal standard discussed above, Applicants submit that one of skill in the art would be convinced from the experimental results described in the Srivastava Declaration that alpha (2) macroglobulin - antigenic molecule complexes can be used to stimulate an immune response and treat or prevent cancer, corroborating the utility of the claimed compositions asserted in the specification of the instant application. This evidence satisfies the legal standard for compliance with the enablement requirement of Section 112, such the one of skill in the art can make and use complexes comprising alpha (2) macroglobulin and an antigenic molecule which displays the antigenicity of an antigen overexpressed in a cancer cell (relative to a noncancerous cell) or an agent of an infectious disease without undue experimentation.

With respect to Point 6 of Paper No. 13, Applicants submit that one of skill in the art would not need to engage in undue experimentation to determine if the compositions of the invention can prevent diseases such as cancer and HIV. To support the Applicants' asserted utility for prevention of disease, Applicants once again invite the Examiner's attention to the Srivastava Declaration submitted herewith, which demonstrates that prevention and/or delaying the onset of cancer was achieved in a mouse model using a composition comprising an alpha (2) macroglobulin and an antigenic molecule displaying the antigenicity of an antigen of a cancer cell.

In addition, Applicants remind the Examiner, that, according to the legal standard discussed above, the claimed compositions meet the Section 112 standard for enablement, if the invention is not "totally incapable of achieving a useful result." *Brooktree v. Advances Micro Devices*, 24 U.S.P.Q.2D 1401, 1412 (Fed. Cir. 1992). The results clearly

show that the claimed complexes of alpha (2) macroglobulin and antigenic molecules can be used to treat and/or prevent cancer.

The Examiner also alleges in Point 6 that animal model systems for drug discovery for cancer are not predictive, and that therefore the specification is not enabled for the full scope of pharmaceutical compositions that comprise compositions that are useful for the prevention of disease. The Examiner is again reminded that the Federal Circuit has stated that animal models are sufficient to establish a credible utility. As explained by the *Brana* Court:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans. *Id.* at 1442 [quoting *In re Krimmel*, 292 F.2d 948, 953 (CCPA 1961)].

Thus, the utility of the claimed compositions asserted in specification, *e.g.*, preventative cancer and infectious disease vaccines, have been convincingly corroborated by the Srivastava Declaration and as such, the Applicants' burden for providing evidence of the asserted utility has been met.

In view of the forgoing reasoning, Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph is in error and respectfully request its withdrawal.

2. THE REJECTION UNDER 35 U.S.C. § 102(b) FOR ANTICIPATION SHOULD BE WITHDRAWN

Claims 1, 7, 8, and 42 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Otto *et al.* (1998, J. Urol. 159(1):297-303; hereinafter "Otto"), which describes a purified complex of alpha (2) macroglobulin non-covalently associated with PSA, which

the Examiner contends is a tumor-specific antigen. Applicants believe this rejection is in error because PSA is properly characterized as a *tumor-associated* antigen and not a *tumor-specific* antigen. Nevertheless, Applicants submit that the rejection has been overcome or obviated by the amendment to the Claims 1, 7, and 8, as discussed below.

Claims 1, 7, and 8 have been amended to exclude PSA from the genus of antigenic molecules comprised by the claimed compositions. In particular, Claims 1, 7, and 8 as amended are drawn to a pharmaceutical composition comprising a non-covalent complex of alpha (2) macroglobulin and an antigenic molecule, a purified molecular complex comprising alpha (2) macroglobulin and an antigenic molecule, or a purified population of molecular complexes comprising alpha (2) macroglobulin and an antigenic molecule, respectively, wherein the antigenic molecule is other than PSA. As such, Otto does not anticipate amended Claims 1, 7, and 8, and claims dependent thereon.

Support for the proposition that claims can be properly amended to exclude a particular species of a genus can be found in *In re Johnson*, 558 F.2d 1008 (1977) [*see also* § 2173.05(i) of the MPEP]. According to the *Johnson* standard, in the present case support for removal of one or more species of from a claim would require a generic disclosure of an antigen overexpressed in a cancer cell relative to its expression in a noncancerous cell of said cell type, coupled with a list of species of such antigens. This genus is defined functionally as any antigen which displays the antigenicity of an antigen overexpressed in a cancer cell relative to its expression in a noncancerous cell of the same cell type, and the specification discloses numerous species within the genus, such as the tumor-specific antigens and tumor associated antigens exemplified in Section 5.2.4.1 (p. 37, *l.* 11-24; *see also* Section 5.3.5.3, at p. 50, *l.* 24 to 51, *l.* 7). According to *Johnson* and the MPEP, this constitutes sufficient support for the proviso in Claims 1, 7, and 8 excluding the species PSA from the genus of

antigens displaying the antigenicity of an antigen overexpressed in a cancer cell relative to its expression in a noncancerous cell of the same cell type.

Thus, Claims 1, 7, 8, and 42, as amended, do not encompass compositions comprising complexes of alpha (2) macroglobulin and PSA, and are therefore not anticipated by Otto.

In view of the reasoning presented above, Otto does not disclose or suggest the claims of the instant invention. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C.§ 102(b) should be withdrawn.

3. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION, SHOULD BE WITHDRAWN

Claims 1, 7, 8, 9, 40, and 42-49 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. In particular, the Examiner asserts that an antigenic molecule that displays the antigenicity of a either a tumor-specifc antigen or an antigen associated with an infectious disease or agent is not adequately described by the instant specification.

Applicants submit that an "antigenic molecule displaying the antigenicity of an antigen overexpressed in a cancer cell relative to its expression in a noncancerous cell of said cell type" and an "antigenic molecule displaying the antigenicity of an antigen associated with an infectious disease or agent" are sufficiently described in the instant application to convey to the skilled artisan that the inventor had possession of the claimed subject matter. In particular, given the high level of skill in the art, sufficient relevant physical, chemical and functional characteristics of such compositions are provided by the specification to satisfy the written description requirement of Section 112.

The test for sufficiency of written description is whether the disclosure of the application 'reasonably conveys to the artisan that the inventor had possession' of the claimed subject matter. *In re Kaslow*, 707 F.2d 1366, 1375, 217 U.S.P.Q. (BNA) 1089, 1096 (Fed. Cir. 1983); accord *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563; *see also*, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575, 227 U.S.P.Q. (BNA) 177, 179 (Fed. Cir. 1985). The Court of Appeals for the Federal Circuit has repeatedly considered the written description requirement and consistently found that exacting detail is not necessary to meet the requirement:

> If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if [not] every nuance of the claims is explicitly described in the specification, the adequate written description requirement is met.

In re Alton, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

The criteria for determining sufficiency of written description set forth in Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description Requirement" ("the Guidelines") (published in the January 5, 2001 Federal Register at Volume 66, Number 4, p. 1099-1111), specifies that:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a) above), reduction to drawings (see (1) (b) above), or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above).

Id. at p. 1106, column 3, *l.* 13-29.

Where the specification discloses any relevant identifying characteristics, *i.e.*, physical, chemical and/or functional characteristics sufficient to allow a skilled artisan to recognize the

applicant was in possession of the claimed invention, a rejection for lack of written description under Section 112, first paragraph, is misplaced.

Furthermore, in accordance with the Guidelines, what is conventional or well known to one of skill in the art need not be disclosed in detail, and, where the level of knowledge and skill in the art is high, a written description question should not be raised. The Guidelines specify that:

> Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. Patents and printed publications in the art should be relied upon to determine whether an art is mature and what the level of knowledge and skill is in the art. In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses *only a method of making the invention and the function* of the invention.
>
> *Id.* at p. 1106, column 2, *ll.* 50-59 (*emphasis added*).

Thus, a rejection for lack of written description is also misplaced where the technology is mature and the level of skill in the art is high and the specification discloses at a minimum a method for making the invention and the function of the invention.

According to the legal standard *supra*, given the high level of skill in the art, sufficient relevant physical, chemical and functional characteristics of antigenic molecules displaying the antigenicity of an antigen overexpressed in a cancer or an antigen associated with an infectious disease or agent are provided by the instant application to convey to the skilled artisan that the inventor had possession of the claimed subject matter. The specification comprehensively identifies the functional characteristics of the claimed pharmaceutical compositions comprising such antigenic molecules. In particular, the claimed

compositions principally function by binding of the alpha (2) macroglobulin-antigenic molecule complex to the alpha (2) macroglobulin receptor, resulting in the antigen being taken up by cells and presented to the immune system to stimulate an immune response (see p. 7, *ll.* 25-35). Functional characteristics of the specified antigenic molecules include, *e.g.*, overexpression in certain cell types, presence in infectious agents, and the ability to stimulate an immune response (see p. 8, *ll.* 13-26 and p. 37, *l.* 5-10).

In addition to functional characteristics, the physical and chemical characteristics of a representative number of the claimed compositions are also provided. Examples of well-characterized antigenic molecules were known in the art and numerous examples of which are provided by the instant specification (see, *e.g.*, Sections 5.2.4.1, 5.2.4.4, 5.2.4.5 and p. 37, *ll.* 12-24, and p. 50, *l.* 31 through p. 51, *l.* 7). The specification also provides an example of a peptide sequence of a known murine leukemia virus gp70-derived H2-Ld-restricted peptide AH-1 (*see* p. 61, *ll.* 25-31, where this peptide is disclosed in the context of gp96 chaperoning of peptides).

However, the Examiner contends that specification describes only tumor antigens and infectious agents, but does not adequately describe antigenic molecules having the antigencity of tumor antigens and infectious agents. The Examiner is reminded that, according to the legal standard *supra,* what is conventional or well known to one of skill in the art need not be disclosed in detail, and, where the level of knowledge and skill in the art is high, the written description requirement should not be raised. In the instant case, numerous well-known techniques for the prediction and analysis of antigenic peptides were sufficiently developed in the art and routinely practiced at the time of filing of the instant application. For example, techniques for epitope identification such as protein hydrophobicity algorithms, protein secondary structure prediction algorithms, T cell epitope prediction (available since

the 1970s), protein hydrophilicity algorithms, protein antigenicity prediction algorithms, and B cell epitope prediction algorithms (available since the 1980s) were routinely in practice. Bioinformatics sequence database searches were developed in the 1990s and were familiar to the skilled artisan as of the filing date (see http://www.epitope-informatics.com/References.htm, Supplemental Information Disclosure Statement "IDS" reference no. ER submitted herewith).

In particular, the Examiner's attention is invited to Pfreundschuh (2000, Cancer Chemother. Pharmacol. 46:S3-7, IDS reference no. EO submitted herewith) which discloses a method for searching for antigens of human cancers by screening of tumor derived expression libraries for antigens and identification by recombinant expression cloning. The technique was successfully used by Obata *et al.* (Cancer Chemother. Pharmacol. 46:S37-42, IDS reference no. EN submitted herewith) to identify both tumor-specific and tumor-associated human stomach cancer antigens. For infectious disease, Ibe *et al.* (1998, J. Gen. Virol. 79:1735-1744, IDS reference no. EM submitted herewith) identified epitopes of hepatitis C virus using reverse immunogenetics (see abstract). Sette *et al.* (1989, Proc. Natl. Acad. Sci. 86:3296-3300, IDS reference no. EQ submitted herewith) disclose algorithms for identification of protein antigens that can be applied to a variety of infectious pathogens such as malaria, influenza, and HIV (see Table 4, p. 3298). Roberts *et al.* (1996, AIDS Res. Hum. Retroviruses 12:593-610, IDS reference no. EP submitted herewith) identified epitopes for use in an HIV vaccine using a computer-driven algorithm, named EpiMer, that identified peptides from protein sequences. The technique was shown to be more efficient than the other antigen identification algorithms such as AMPHI and the well known standard technique of synthesizing short overlapping peptides and testing them for immunogenicity.

Thus, the level of skill and knowledge in the art was such that production of an antigenic molecule displaying a specified antigenicity was considered conventional at the time of filing of the instant application. Given the mature technology, the complete functional description of the claimed antigenic molecule and the structural description, including representative examples of antigenic molecules of tumor antigens, infectious disease agents, and a molecule having the antigenicity of an infectious agent, one of skill in the art would have readily appreciated that the Applicants were in possession of the invention.

Thus, Applicants submit that the description of the claimed pharmaceutical compositions capable of treating or preventing a disease comprising an alpha (2) macroglobulin complexed to an antigenic molecule displaying the antigenicity of either an antigen overexpressed in a cancer cell relative to its expression in a noncancerous cell of said cell type or an antigen associated with an infectious disease or agent fully satisfies the written description requirement of Section 112. As such, Applicants submit that the rejection of Claims 1, 7, 8, 9, 40, and 42-49 under 35 U.S.C. § 112, first paragraph, for lack of written description is in error and request its withdrawal.

CONCLUSION

Applicants respectfully request that the foregoing amendments and remarks in be made of record in the instant application. Applicants estimate that the remarks made herein now place the pending claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

It is believed that no additional fee is required for filing this paper. In the event a fee is required, please charge the required fee to the Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date: April 5, 2004

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Enclosures